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Health Effects Assessment for 2,4,5-Trichlorophenoxy Acetic Acid (2,4,5-T)

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HEALTH EFFECTS ASSESSMENT FOR 2,4,5-TRICHLOROPHENOXY ACETIC ACID (2,4,5-T)

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 2,4,5-T. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1981. Risk Assessment on (2,4,5-Trichlorophenoxy) Acetic Acid, (2,4,5-T), 2,4,5-Trichlorophenoxy Propionic Acid, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). EPA 600/6-81-003. NTIS PB 81-234825.

U.S. EPA. 1988. Integrated Risk Information System (IRIS). Reference Dose for Oral Exposure for 2,4,5-Trichlorophenoxy Acetic Acid (2,4,5-T). Online. (Verification date 01/20/88.) Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the RfD (reference dose). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route-specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The data base for 2,4,5-T contained several subchronic toxicity studies and teratogenicity/reproductive effects studies, but there was relatively little useful chronic toxicity information. There were, however, two long-term studies using rats, a 2-year feeding study and a 3-generation reproductive effects study, that both defined a NOEL of 3 mg/kg. This value from the 2-year dietary study using rats (Kociba et al., 1979) was used as the basis for an oral RfD of 2 mg/day (U.S. EPA, 1988). The maximum CS that could be calculated from chronic toxicity data was 28 and was derived from a 2-year feeding study using mice in which 12 mg/kg/day resulted in decreased survival time (Muranyi-Kovacs et al., 1976). A subchronic rat NOEL of 10 mg/kg/day (Gehring and Betso, 1978) was used as the basis for an RfD_S of 7.0 mg/day. The available information was judged to be inadequate for evaluating the carcinogenicity of 2,4,5-T and inhalation RfDs.

TABLE OF CONTENTS

	Page
1. ENVIRONMENTAL CHEMISTRY AND FATE	1
2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	4
2.1. ORAL	4
2.2. INHALATION	4
3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	5
3.1. SUBCHRONIC	5
3.1.1. Oral	5
3.1.2. Inhalation	6
3.2. CHRONIC	6
3.2.1. Oral	6
3.2.2. Inhalation	7
3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	8
3.3.1. Oral	8
3.3.2. Inhalation	18
3.4. TOXICANT INTERACTIONS	18
4. CARCINOGENICITY	19
4.1. HUMAN DATA	19
4.1.1. Oral	19
4.1.2. Inhalation	19
4.2. BIOASSAYS	19
4.2.1. Oral	19
4.2.2. Inhalation	20
4.3. OTHER RELEVANT DATA	21
4.4. WEIGHT OF EVIDENCE	21
5. REGULATORY STANDARDS AND CRITERIA	22

TABLE OF CONTENTS

	Page
6. RISK ASSESSMENT	23
6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)	23
6.1.1. Oral	23
6.1.2. Inhalation	23
6.2. ACCEPTABLE INTAKE CHRONIC (AIC)	24
6.2.1. Oral	24
6.2.2. Inhalation	26
6.3. CARCINOGENIC POTENCY (q_1^*)	26
7. REFERENCES	27
APPENDIX: Summary Table for 2,4,5-T	38

LIST OF TABLES

No.	Title	Page
1-1	Selected Physical and Chemical Properties and Environmental Fate for 2,4,5-T.	2
3-1	Studies on the Potential Teratogenic Effects of 2,4,5-T and its Esters Administered to Mice by Gavage.	9
3-2	Studies on the Potential Teratogenic Effects of Orally Administered 2,4,5-T and its Esters to Rats.	12
3-3	Studies on the Potential Teratogenic Effects of 2,4,5-T in Other Experimental Mammals Treated Orally.	14
6-1	Composite Scores for the Toxicity of 2,4,5-T by Oral Exposure	25

LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CS	Composite score
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ED_{50}	Dose effective to 50% of the recipients
LOAEL	Lowest-observed-adverse effect level
LOEL	Lowest-observed-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cells
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
SAP	Serum alkaline phosphatase
SGPT	Serum glutamic pyruvic transaminase
TLC	Thin-layer chromatography
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fate of 2,4,5-T are presented in Table 1-1.

In the atmosphere, 2,4,5-T should exist partly in vapor form, and partly as adsorbed matter on air-borne particulates as a result of vapor phase adsorption or wind erosion of treated soil (Norris, 1981). 2,4,5-T has the potential to undergo direct photolysis from UV adsorption at >290 nm (Plimmer, 1972), reaction with photochemically generated HO radical (U.S. EPA, 1986a) or physical removal by settling or washout in rainfall (Norris, 1981). The atmospheric half-life listed in Table 1-1 is based on the vapor phase hydroxyl reaction rate constant of 4.59×10^{-13} cm^3/molecule/sec at 25°C and an ambient HO radical concentration of 8.0×10^5 molecule/cm^3 (U.S. EPA, 1986a). In water, photochemical decomposition and biodegradation appear to be the dominant fate mechanisms. The aquatic near-surface photolysis half-life during summer at latitude 40°N has been calculated to be 15 days. The presence of humic substances greatly enhances the photoreaction. In acidic, weakly absorbing natural water, iron and peroxides may also catalyze the photoreaction (Skurlatov et al., 1983).

Data regarding the microbial degradation of 2,4,5-T in soil suggest that biodegradation may also contribute significantly to the degradation of 2,4,5-T in aquatic systems. Adsorption to suspended solids and sediments may be significant since humic acids found in almost all water and soil systems have been shown to strongly adsorb 2,4,5-T from solution (Wershaw et al., 1969). Bioaccumulation in aquatic organisms should not be significant.

TABLE 1-1

Selected Physical and Chemical Properties and Environmental Fate for 2,4,5-T

Property	Value	Reference
CAS number:	93-76-5	
Chemical class:	halogenated phenoxy acid herbicide	
Molecular weight:	255.5	
Vapor pressure:	NA	
Water solubility:	268 mg/ℓ at 25°C	Que Hee et al., 1981
Log octanol/water partition coefficient:	3.13	Hansch and Leo, 1985
pKa:	2.88	Que Hee et al., 1981
Bioconcentration factor:	2- 3 (estimated) 2.3	Kenaga, 1980; Garten and Trabalka, 1983
Soil adsorption coefficient:	186	Nkedi-Kizza et al., 1983
	53-220	Kenaga, 1980
Half-lives in Air:	>1 day (estimated for vapor phase)	U.S. EPA, 1986a
Water:	<15 days (estimated)	Skurlatov et al., 1983; Lyman et al., 1982
Soil:	30-208 days	McCall et al., 1981; O'Connor and Wieranga, 1973; Altom and Stritzke, 1973; Bovey and Baur, 1972

NA = not available

In soil, 2,4,5-T is expected to biodegrade (Rosenburg and Alexander, 1980; Byast and Hance, 1975). The persistence of 2,4,5-T in soil is reported to vary from 14-300 days depending upon climatic conditions and type of soil, but usually does not exceed one full growing season regardless of the application rate (McCall et al., 1981; O'Connor and Wieranga, 1973; Altom and Stritzke, 1973; Bovey and Baur, 1972). Measured TLC R_f values of 0.17 for muck, 0.48 for clay, 0.54 for silt clay loam and 0.73-0.89 for sandy loam (Helling, 1971) suggest that 2,4,5-T mobility would vary from highly mobile in sandy soil to slightly mobile in muck (Reinbold, 1979).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

It has been reported that 2,4,5-T is rapidly and efficiently absorbed from the gastrointestinal tract of mammals, ≤98-100% after small doses (Erne, 1966; NRCC, 1978). Over 90% of single oral doses of 2,4,5-T (0.04-200 mg/kg) were absorbed from the gastrointestinal tract of rats (Fang et al., 1973; Piper et al., 1973). Eaton (1982) found that reabsorption of biliary-excreted 2,4,5-T was almost complete. Ferry et al. (1982) reported that two human volunteers who ingested 1 mg of 2,4,5-T excreted 83.8 and 88.5% of the dose in the urine within 48 hours, suggesting that at least that much had been absorbed from the gastrointestinal tract.

Gehring et al. (1973) conducted a pharmacokinetics study in which oral doses of 5 mg/kg were administered to five volunteers and essentially all of the 2,4,5-T was absorbed from the gastrointestinal tract. Plasma 2,4,5-T concentration appeared to be associated with first-order rates of absorption and clearance. Applying a first-order model to the data, absorption constants were calculated for each of the five subjects. These constants ranged from 0.450 ± 0.045 to 2.487 ± 0.225 hour^{-1}, corresponding to a $t_{1/2}$ of 0.75 hour.

On the basis of their low water solubility and by comparison with 2,4-D, esters of 2,4,5-T would probably be absorbed less readily than the acids and salts (Que Hee et al., 1981).

2.2. INHALATION

Burton et al. (1974) studied absorption of various herbicides from the rat lung by administering them in Krebs-Ringer solution through a tracheal cannula. The time necessary for 50% absorption of the administered 2,4,5-T was 1.7 minutes. Lipid solubility appeared to be the primary factor in determining rate of absorption.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. A consideration in evaluating 2,4,5-T toxicity data is that the compound is usually formulated as a salt or ester in herbicides. These salts and esters are rapidly hydrolyzed to the acid in animals, however, so that their toxicity is generally attributable to the parent acid (Gehring and Betso, 1978).

One of the major problems in assessing the effects of 2,4,5-T is the contamination with varying amounts of 2,3,7,8-TCDD. Many investigators were unaware of the presence and amount of 2,3,7,8-TCDD in a sample and, therefore, this information has gone unreported in many studies. Consequently, whether the reported effects are attributable to 2,4,5-T alone, the 2,3,7,8-TCDD contaminant, a combination of both, or additional contaminants such as the carrier of emulsifier is not clear in many studies.

Results from several unpublished subchronic oral toxicity studies by Dow Chemical Company have been reported in brief form. In 90-day rat studies, monopropylene, dipropylene and tripropylene glycol butyl ether esters of 2,4,5-T at 186 and 62 mg/kg/day caused unspecified toxic effects, while no toxic effects occurred at 18.6 mg/kg/day (Advisory Committee on 2,4,5-T, 1971; NAS, 1977). In another 90-day study, groups of Sprague-Dawley rats were fed diets containing the acid form of 2,4,5-T that provided doses of 0, 3, 10, 30 or 100 mg/kg/day (Gehring and Betso, 1978). Depression in body weight gain accompanied by decreased food intakes, elevated SAP in both sexes and SGPT in males and decreased RBC counts and blood hemoglobin concentration in males, was observed at 100 mg/kg/day. Necropsy revealed pale livers with hepatocellular swelling. At 30 mg/kg/day 2,4,5-T caused increased relative liver and kidney weights and elevated SGPT and SAP

levels. No adverse effects were reported at 10 and 3 mg/kg/day (Gehring and Betso, 1978; NAS, 1977). In another 90-day rat study, 100 mg/kg/day 2,4,5-T containing TCDD at 0.5 ppm caused decreased growth and changes in serum enzyme concentrations, while no adverse effects were reported at 3, 10 and 30 mg/kg/day (Advisory Committee on 2,4,5-T, 1971). Further details were not provided. The Weed Science Society of America (1979) reported 10 mg/kg/day as a 90-day NOEL for rats and dogs, but no details were given.

Drill and Hiratzka (1953) administered canned dog food containing 2,4,5-T in gelatin capsules to groups of 1-2 mongrel dogs/sex at 0, 2, 5, 10 or 20 mg/kg, 5 days/week for 90 days. Dogs receiving daily oral doses of 2, 5 or 10 mg/kg suffered no adverse effects, but four dogs receiving 20 mg/kg died during the experiment. Dogs are much more sensitive to the effects of orally-administered 2,4,5-T than rodents, probably because of a decreased capacity for renal excretion of the compound.

3.1.2. Inhalation. Pertinent data regarding subchronic toxicity of 2,4,5-T in inhalation exposures could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Kociba et al. (1979) conducted a 2-year study in which groups of 50 male and 50 female Sprague-Dawley rats consumed diets containing 2,4,5-T that provided dosages of 3, 10 or 30 mg/kg/day. Parameters of toxicity that were evaluated included appearance and behavior, food consumption, body weight, mortality, hematology, clinical chemistries, urinalysis, and gross and microscopic pathology. Rats receiving the high dosage experienced decreased body weight gain, increased relative kidney weight, increases in total urine volume, urinary coproporphyrins and uroporphyrins, and morphological changes in kidneys, liver and lungs. Liver effects

included an increased incidence of periportal inflammation, focal biliary hyperplasia and inflammation. Mild kidney effects occurred at 10 mg/kg/day, including increased urinary excretion of coproporphyrins in males at 4 months and a mild increase in the incidence of mineralized deposits in the renal pelvis of females after 2 years. No treatment-related effects occurred at 3 mg/kg/day.

Muranyi-Kovacs et al. (1976) conducted a 2-year study in which two strains of mice were fed 2,4,5-T (dioxin content <0.05 ppm). Male and female XVII/G and C3Hf mice were provided with drinking water containing 100 mg/ℓ (ppm) from 6 weeks of age for the next 2 months. From then until death, 2,4,5-T was provided only in the diet at 80 ppm. According to the authors, this resulted in a dosage of ~12 mg/kg/day. Effective numbers of mice, those surviving ≥300 days or those developing a tumor at <300 days, ranged from 19-44. Survival time of male C3Hf mice was decreased, but no other toxic effects were reported.

3.2.2. Inhalation. There have been several epidemiological studies concerning occupational exposure to 2,4,5-T, but most of these were concerned with cancer incidence and few threshold toxicity data were provided. Suskind and Hertzberg (1984) found an increased incidence of chloroacne among 204 workers exposed to 2,4,5-T relative to 163 unexposed workers (55.7% vs. 0%). There was also an association between exposure and history of gastrointestinal tract ulcers. Pulmonary function values among exposed workers who smoked were lower than those in unexposed workers who smoked. There was no evidence of increased risk of cardiovascular disease, hepatic or renal disease, or nervous system problems. Exposures were not quantitated and all of the workers in the study were currently or had been exposed to other chemicals.

Chronic inhalation bioassays with 2,4,5-T could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Several studies concerning the teratogenicity of 2,4,5-T are included in Tables 3-1 to 3-3, but only studies that define thresholds or address critical issues are discussed in the text.

Several teratogenicity studies with mice are summarized in Table 3-1. The most consistent teratogenetic effect noted was cleft palate, which occurred in the majority of the experiments (Neubert and Dillmann, 1972; Roll, 1971; Courtney, 1977; Courtney et al., 1970a,b; Gaines et al., 1975; Chernoff and Kavlock, 1982). TCDD, a common contaminant of 2,4,5-T, is a known teratogen associated with the development of cleft palates in mice. In order to estimate the contribution of TCDD to the incidence of cleft palate observed in 2,4,5-T-treated mice, Neubert and Dillmann (1972) conducted teratogenicity studies with 2,4,5-T samples of different TCDD content (samples A, B or C, Table 3-1) and with TCDD itself. They calculated ED_{50} values for incidence of cleft palate using the litter as the experimental unit and found that the ED_{50} values for 2,4,5-T samples A and B were much lower than would be expected if TCDD alone were responsible for the teratogenic activity. The estimated ED_{50} values, however, indicated a more than additive response, but it is not clear from these results if 2,4,5-T itself is teratogenic or if it synergizes the teratogenic action of TCDD. The induction of cleft palate has been demonstrated in three studies in which relatively pure 2,4,5-T was used (TCDD content $\leq$0.05 ppm) (Neubert and Dillmann, 1972; Roll, 1971; Courtney, 1977), suggesting that some teratogenic activity must be due to 2,4,5-T itself or contaminants other than TCDD. In these studies, the highest NOEL for cleft palate induction was 30 mg/kg (Neubert and Dillmann, 1972) and the LOEL was 35 mg/kg (Roll, 1971).

TABLE 3-1

Studies on the Potential Teratogenic Effects of 2,4,5-T and Its Esters Administered to Mice by Gavage

Strain	Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
[redacted]	rape-seed oil	acid	<0.02 ppm (Sample A)	8, 15, 30, 45, 60, 90 and 120 mg/kg	6-15	18	no toxic effects; decreased maternal weight at doses ≥90 mg/kg	Significant increases in the incidence of cleft palates at doses above 30 mg/kg; significantly decreased ($p<0.005$) fetal weight at all dose levels.	Khera and Billmann, 1972
	rape-seed oil	acid	0.05±0.02 ppm (Sample B)	30, 60 and 90 mg/kg	6-15	18	no toxic effects; decreased maternal weight at 90 mg/kg	Increases in the incidence of cleft palate at 60 and 90 mg/kg; significant ($p<0.005$) at all dose levels	
	rape-seed oil	acid	NR (commercial) (Sample C)	90 mg/kg	6-15	18	no toxic effects; but decreased maternal weight	Increase in the incidence of cleft palate; significant ($p<0.005$) decrease in fetal weight	
	rape-seed oil	butyl ester	NR	12 and 17 mg/kg	6-15	18	no toxic effects	Significant decrease in fetal weight but no effect on mortality; increase in frequency of cleft palate similar to that seen with acid	
	NR	acid	0.05±0.02 ppm	20, 35, 60, 90 and 130 mg/kg	6-15	NR	toxic effects; observed at 90 and 130 mg/kg	Increases in the percentage of resorptions and dead fetuses at 90 and 130 mg/kg; increases in the incidence of cleft palate and retardation of skeletal development at 35 mg/kg and above	Roll, 1971
CD-1	corn oil: acetone (9:1)	acid	<0.05 ppm	115 mg/kg	10-15	18	no significant effect on weight gain or liver-to-body weight ratios	No effect on fetal mortality or fetal weight but an increase in the incidence of cleft palate	Courtney, 1977

07/14/83

TABLE 3-1 (cont.)

Strain	Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
NMRI	arachis oil	acid	<0.1 ppm	20, 40, 80 and 120 mg/kg	6-15	NR	unspecified maternal toxicity at 80 and 120 mg/kg	Fetal death and unspecified malformations at 80 and 120 mg/kg	Frohberg et al., 1974
NMRI	arachis oil	butoxy-ethyl ester	20, 40, 80 and 120 mg/kg	6-15	NR	NR	NR	Unspecified malformations and fetal death only in 120 mg/kg dose group	Frohberg et al., 1974
CD-1	corn oil	acid	<0.05 ppm	20 and 100 mg/kg	6-15	offspring sacrificed 62±2 days after birth	pronounced mortality at the high dose level	Significant ($p<0.05$) decrease in average birth weight in the high-dose group; significant increase in the frequency of stillborns in both dose groups; subtle but significant ($p<0.05$) skeletal variations, but no indication of cleft palate, in fully ossified high-dose group adults; effects primarily involved frontal bones of skull and cervical vertebrae (e.g., occurrence of foramina transversia imperfecta in cervical vertebrae #1 and #2, dysymphysis of second cervical, shift of the arch foramina from cervical vertebrae #4 to #5, loss of thoracic vertebrae #2 dorsal spine, reduced number of caudal vertebrae.	Beck, 1981
C57Bl/6	honey: water (1:1)	acid	30 ppm	46.4 and 113 mg/kg	6-14	18	NR	Significant ($p<0.01$) increases in the incidence of cleft palate in the high-dose group and cystic kidney in both dose groups; increased fetal mortality also observed in the high-dose group	Courtney et al., 1970a,b

07/14/89

TABLE 3-1 (cont.)

Strain	Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
AKR	honey: water (1:1)	acid	30 ppm	113 mg/kg	6-15	19	increase in liver-to-body weight ratio	Significant ($p<0.95$) increase in the incidence of cleft palate and fetal mortality	Courtney et al., 1970a,b
A/JAX	NR	acid	NR	15-120 mg/kg	6-14	NR	NR	Increases in the incidence of cleft palate at all dose levels; ED_{50} for cleft palate of 25 mg/kg	Gaines et al., 1975
C57Bl/6 C3H/He BALB/c and CD-1	NR	acid	NR	15-120 mg/kg	6-14	NR	NR	Increases in the incidence of cleft palate at doses of 30 mg/kg and above for all strains; ED_{50} for cleft palate in BALB/c mice was 105 mg/kg, which was significantly ($p<0.05$) higher than the ED_{50} in A/JAX mice	
CD-1	corn oil	acid	NR	130 mg/kg	8-12	1 and 3 postnatal	maternal weight loss	Decreased survival; cleft palate	Chernoff and Kavlock, 1982

NR = Not reported

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TABLE 3-2

Studies on the Potential Teratogenic Effects of Orally Administered 2,4,5-T and Its Esters to Rats[a]

Strain	Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Sprague-Dawley	NS	acid	NS	1, 3, 6, 12, 24 and 50 mg/kg/day	6-15	NS	"no clinical or gross pathologic signs of toxicity"	"...litter size, number of resorptions, birth weights and sex ratios were unaffected by chemical treatment; detailed visceral and skeletal examinations did not reveal teratogenic effects."	Thompson et al., 1971
Sprague-Dawley	NS	acid	NS	100 mg/kg/day	6-15	NS	"maternal toxicity and death signs of toxicity"	"4/25 pregnant rats survived; 3 had complete early resorptions and 1 had a viable litter of 13 fetuses which showed toxic effects but no terata."	Thompson et al., 1971
Sprague-Dawley (groups of 25 rats)	hydroxy-propyl-methyl-cellulose	acid	0.5 ppm	1, 3, 6, 12 or 24 mg/kg/day	6-15	20	no effect on body weight and no observable signs of toxicity	A slight but statistically significant ($p<0.05$) decrease in implantations and litter size in lowest dose group only; no frank teratogenic effects based on a detailed examination of the control and 24 mg/kg dose group; the only effect noted was an increase in the incidence of 5th partially ossified sternebrae.	Emerson et al., 1970, 1971[b]
Wistar	aqueous gelatin or corn oil	acid	<0.5 mg/kg	25, 50, 100 or 150 mg/kg/day	6-15	22	some maternal mortality and decreased body weight gain at 150 mg/kg; no signs of toxicity at 100 mg/kg or below	At 100 or 150 mg/kg, decreased fetal weight, increased fetal mortality and an increase in the incidence of skeletal anomalies; no significant effect at the two lower dose levels.	Khera and McKinley, 1972; Khera et al., 1971
	aqueous gelatin or corn oil	butyl ester	<0.5 mg/kg	50 or 150 mg/kg/day	6-15	22	NR	No significant effect on fetal mortality, fetal weight, or the incidence of anomalies	Khera and McKinley, 1972; Khera et al., 1971
Wultzman	1:1 solution of honey and water	acid	30 ppm	4, 6, 10.0 and 46.4 mg/kg/day	10-15	20	NR	Significant ($p<0.01$) increases in fetal mortality at the two higher dose levels; dose-related increases in the percent of abnormal fetuses/litter; a high incidence of cystic kidneys in treated groups.	Courtney et al., 1970a,b

07/14/89

TABLE 3-2 (cont.)

Strain	Vehicle	Form of 2,4,5-T	TCDD Level	Daily Dose	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
CD	15% sucrose solution	acid	0.5 ppm	10.0, 21.5, 46.4 and 80.0 mg/kg/day	6-15	20	reduced maternal weight gain at the two higher dose levels ($p<0.05$) and increased liver-to-body weight ratio at the highest dose level ($p<0.05$)	Increase in the incidence of kidney anomalies but no increase in cleft palate	Courtney and Moore, 1971
NS, from Rappolovo Nursery, USSR	aqueous emulsion with Tween-20 and Tween-40	acid	NS	100 and 400 mg/kg	1-14 or 1-16	19-20	NS	Dose-related increase in embryonic mortality; lower dose induced the following combination of deformities: absence of lower jaw, changes in hind limbs and exophthalmos; high dose induced cleft palate, hydrocephalus, hydronephrosis and changes in the upper limbs	Sokolik, 1973
NS, from Rappolovo Nursery, USSR	aqueous emulsion with Tween-20 and Tween-40	butyl ester	NS	50 and 200 mg/kg	1-14 or 1-16	19-20	NS	High mortality among embryos at both dose levels; dose-related increase in the incidence of cleft palate	Sokolik, 1973
NS	methocel	acid	0.5 ppm	50 mg/kg	6-15	NS	no effect on mortality or body weight gain	No significant effect on fetal mortality or fetal weight; a significant ($p<0.05$) increase in the incidence of delayed ossification	Sparschu et al., 1971
	methocel	acid	0.5 ppm	100 mg/kg	6-10	NS	increased mortality and decreased body weight gain	Increase in the incidence of delayed ossification and poorly ossified or maligned sternabrae ($p<0.05$)	Sparschu et al., 1971
NS	NS	acid	NS	200 and 400 mg/kg	NS	NS	NS	High embryo mortality (up to 40%) at high dose. Altered cleavage rates and chromosome aberrations in developing embryos following administration of 400 mg/kg prior to ovulation.	Chebotar, 1980

[a] Source: U.S. EPA, 1981

[b] This appears to be a more complete publication of Thompson et al. (1971).

NS - Not specified; NR - not reported

TABLE 3-3

Studies on the Potential Teratogenic Effects of 2,4,5-T in Other Experimental Mammals Treated Orally

Animal	Vehicle	Form of 2,4,5-T	TCDD Level (ppm)	Daily Dose (mg/kg)	Treatment Days	Days of Development	Maternal Response	Fetal Response	Reference
Syrian Hamsters *Mesocricetus auratus*	acetone, corn oil, and carboxymethyl cellulose in ratio of 1:5:8:10	acid	<0.1-4.5	20, 40, 80 and 100	6-10	14	NS	Dose-related increases in fetal mortality, gastrointestinal hemorrhages, and fetal abnormalities	Collins and Williams, 1971
Rabbits, New Zealand white 2.6-4.0 kg Groups of 20	gelatin capsule, corn oil	acid	0.5	10, 20 or 40	6-18	29	no effect on maternal weight gain	Significant ($p<0.05$) decrease in mean viable litter size at highest dose level; no other significant dose-related effects; no increase in the incidence of skeletal or visceral abnormalities	Emerson et al., 1971; Thompson et al., 1971
Lambs	ground alfalfa meal	acid	1.0	100	14 36	NS	NS	No congenital deformities in any lambs from 11 treated ewes	Binns and Balls, 1971
		acid	1.0	113	14 19	NS	NS	No congenital deformities in lambs from one treated ewe	
			1.0	113	14 27	NS	NS	No congenital deformities in lambs from two treated ewes	
			1.0	113	14-29	NS	NS	No congenital deformities in lambs from two treated ewes	
		"propylene butyl ether esters"	1.0	100	14 36	NS	NS	No congenital deformities in any lambs from 11 treated ewes	

TABLE 3-3 (cont.)

Animal	Vehicle	Form of 2,4,5-T	TCDD Level (ppm)	Daily Dose (mg/kg)	Treatment Days	Days of Development	Maternal Response	Fetal Response	Reference
Monkey (*Macaca mulatta*) 10 animals in each treated group and 10 in control group	gelatin capsule	acid	<0.05	0.05	22-38	pregnancies allowed to go to term	no signs of toxicity based on hematology, clinical chemistry, and urinalysis data obtained in all females before and immediately after dosing and at 2-month intervals until parturition	All 10 of the treated females gave birth to normal babies	Dougherty et al., 1973, 1975
				1.0	22-38			3/10 treated monkeys delivered live offspring; there was one stillborn fetus and one abortion	
				10.0	22-38			8/10 monkeys delivered live offspring; there were two abortions. HD: Of 10 control monkeys, 9 delivered live offspring; detailed examination of the live infants and the stillborn fetus, including skeletal X-ray studies, revealed no gross developmental abnormality in any of the groups	
Rhesus monkeys	NR	acid	NR	40, 3 times/week	20-48	100	NR	3/4 monkeys delivered normal offspring; one monkey aborted	Wilson, 1971

NS = Not specified; NR = not reported

07/14/89

The apparent NOEL might be an artifact resulting from the difficulties in detecting statistically significant increases in responses in small groups of animals rather than a lack of teratogenic activity at these doses. Neubert and Dillmann (1972) reported that doses as low as 8 mg/kg by gavage had been shown to cause a significant decrease in fetal body weight in mice.

Several other studies involved the use of 2,4,5-T samples containing higher or unknown levels of TCDD contamination, making them less useful for risk assessment; however, these studies pointed out that the teratogenic potency in mice varied with the strain of mice used, the dosing schedule, and the vehicle. Based on data presented in Table 3-1 and on other data in mice, it can be concluded that 2,4,5-T was more teratogenic in A/JAX mice than in the other strains tested; that treatment on gestation days 11-14 produced a greater teratogenic response than did treatment on gestation days 11-13 or 12-15 at the same or higher doses; and that administration as a solution in DMSO led to a far greater response than did administration as a suspension in sucrose solution.

The effect of the chemical form in which the 2,4,5-T was administered on teratogenic potency to mice was less clear. Frohberg et al. (1974) suggested that the butoxyethyl ester is less potent than the acid, but Neubert and Dillmann (1972) reported similar potencies for the acid and the butyl ester. No firm conclusion can be drawn, however, because the TCDD content of these esters was not reported.

Several studies with rats are presented in Table 3-2. A review of these studies indicates that at doses of $\geq$100 mg/kg/day, 2,4,5-T containing $\leq$0.5 ppm TCDD may cause maternal toxicity, fetotoxicity and skeletal anomalies. In most cases these skeletal anomalies were relatively mild and included

wavy ribs, fused sternum. poor ossification and maligned sternebrae (Emerson et al., 1970, 1971; Khera and McKinley, 1972; Khera et al., 1971; Sparschu et al., 1971). These data suggest that rats are less sensitive to the teratogenic effects of 2,4,5-T than mice, in which doses >35 mg/kg consistently produced cleft palates. In the rat studies, a dosage of 25 mg/kg/day on days 6-15 of gestation appears to be a NOEL for teratogenic and fetotoxic effects.

Smith et al. (1981) conducted a 3-generation study in which 2,4,5-T (TCDD content <0.03 ppb) was administered in the diet to groups of 10-16 male and 20-32 female SD rats at dosages of 0, 3, 10 and 30 mg/kg/day. Rats were 4-6 weeks old initially and were fed the diet for 90 days before mating. The F_1 and F_2 rats were mated at the age of ~130 days. No treatment-related effects on food consumption, body weight gain, behavior, appearance, organ weights, or histological appearance of liver, kidneys and thymus of weanlings were observed. There were no consistent treatment-related effects on fertility index, litter size at birth, weanling body weights or sex ratio of offspring. Reduced 21-day survival of pups was observed in the 10 and 30 mg/kg/day groups. No adverse effects on reproduction occurred at 3 mg/kg/day. No treatment-related teratogenic effects occurred at any dosage.

Teratogenicity studies with other species were summarized in Table 3-3. Collins and Williams (1971) studied teratogenic effects of different 2,4,5-T samples (TCDD content <0.1-4.5 ppm) in hamsters and found that increasing TCDD levels were associated with decreased fetal viability and increased incidences of abnormalities/litter. Highly purified 2,4,5-T still caused abnormalities at doses of 100 mg/kg and caused decreased viability at 40 mg/kg. The studies with other species in Table 3-3 were essentially

negative for teratogenic effects. Dougherty et al. (1973, 1975; and Wilson (1971) did not observe teratogenic effects in primates receiving doses ≤40 mg/kg.

3.3.2. Inhalation. Several studies have related exposure to 2,4,5-T to increases in birth defects and abortions in human populations. A positive association was found in populations in Oregon (U.S. EPA, 1979), New Zealand (Hanify et al., 1981) and Australia (Field and Kerr, 1979). No association was found in Arkansas (Nelson et al., 1979), Hungary (Thomas, 1980), New Zealand (Department of Health, New Zealand, 1980; McQueen et al., 1977; Smith et al., 1982) and Australia (Aldred, 1978). These studies do not demonstrate conclusively that 2,4,5-T is teratogenic or fetotoxic in humans. Pearn (1985) concluded that no epidemiological data indicate that 2,4,5-T causes congenital malformations in humans. The normal problems with epidemiological data are compounded by the difficulty in distinguishing effects of 2,4,5-T from those of TCDD.

Only one animal study concerning inhalation exposures to 2,4,5-T was found, but it was available only as an abstract. In this study, the butoxyethyl ester of 2,4,5-T caused unspecified malformations in NMRI mice at ≥216 mg/m³ (140.4 mg/kg/day; assuming a body weight of 30 grams and a continuous exposure) (Frohberg et al., 1974).

3.4. TOXICANT INTERACTIONS

Although epidemiologic studies have been performed with the chlorophenoxy herbicides (Section 4 1.2.), these studies did not investigate the interactive effects of these compounds. Neubert and Dillmann (1972) investigated the interactions of TCDD and 2,4,5-T in teratogenesis in mice. It was not clear if 2,4,5-T potentiated the teratogenicity of TCDD or if 2,4,5-T was teratogenic by itself (see Section 3.3.1.).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Data concerning carcinogenicity of 2,4,5-T to humans from oral exposure could not be located in the available literature.

4.1.2. Inhalation. There is much data associating exposure to phenoxy acid herbicides and the incidence of cancer in humans. A detailed discussion of this information is beyond the scope of this document, but reviews and evaluations have been done by IARC (1982). Scandinavian epidemiologic studies summarized by IARC (1982) indicated that occupational exposure to phenoxy acid herbicides was associated with an excess risk of the development of soft-tissue sarcomas and malignant lymphomas. As was the case with other epidimiological data, it is impossible to separate effects of 2,4,5-T from those of other phenoxy acid herbicides and TCDD; furthermore, the lengths of exposure and exposure levels were unknown. Thus, these studies are not useful for quantitative risk assessment.

4.2. BIOASSAYS

4.2.1. Oral. There are relatively few studies concerning carcinogenicity of 2,4,5-T in animals. In one study (Bionetics Research Laboratories, Inc., 1968; Innes et al., 1969), groups of 18 male and 18 female mice of each of two strains (B6C3F1 and B6AKF1) received gavage doses of 21.5 mg/kg/day 2,4,5-T (TCDD content not specified) on days 7-28 of age, and then were fed a diet containing 60 ppm 2,4,5-T for 18 months. There was an increased incidence of hepatomas in treated male B6C3F1 mice relative to controls, but this was not statistically significant. No other treatment-related effects on tumor incidence were observed.

Muranyi-Kovacs et al. (1976) exposed groups of C3HF and XVII/G mice to 2,4,5-T (TCDD content <0.05 ppm) in drinking water at 100 mg/L (19 mg/kg/day) for 2 months starting at 6 weeks of age and then in the diet at 80 ppm (15.2 mg/kg/day) until the mice died or were sacrificed when moribund. Total tumor incidence was increased in treated C3HF mice, but this increase was statistically significant only in treated females. Unusual types of tumors appeared relatively early in the life of the treated C3HF mice compared with controls; the authors interpreted this as an indication of the carcinogenicity of 2,4,5-T in mice. No specific target organ was affected, but there was a generalized increase in rare tumors in treated C3HF mice.

Kociba et al. (1979) exposed groups of 50 male and 50 female SD rats to 2,4,5-T (TCDD content <0.33 ppb) in the diet that provided dosages of 3, 10 or 30 mg/kg/day for 2 years. The authors found no treatment-related increase in any type of tumor. A re-evaluation of the histological samples and statistical analyses, however, revealed a statistically significant increase in squamous cell carcinoma of the tongue in male rats receiving 30 mg/kg/day (U.S. EPA, 1981). U.S. EPA (1981) reviewed a similar or perhaps the same study with rats receiving these doses in the diet and reported a statistically significant increase in testicular tumors in treated rats, but stated that these results were questionable. U.S. EPA (1981) concluded that their re-evaluation of the Kociba et al. (1979) data provided "highly suggestive" evidence of the carcinogenicity of essentially pure 2,4,5-T; however, no final judgement or quantitative carcinogenicity risk assessment was made because similar findings were not reported in other studies.

4.2.2. Inhalation. Inhalation carcinogenicity bioassays could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Bionetics Research Laboratories, Inc. (1968) reported that single subcutaneous injections of 215 mg/kg 2,4,5-T (98% pure) in dimethyl sulfoxide at 28 days of age had no effect on tumor incidence in groups of 18 male and 18 female B6C3F1 and BGAKF1 mice.

Negative results have generally been obtained with 2,4,5-T in bacterial mutagenicity assays. Results in other assays, including yeast, *Drosophila*, mouse dominant lethal assays, and *in vivo* and *in vitro* mammalian mutagenicity assays were mixed (U.S. EPA, 1981).

4.4. WEIGHT OF EVIDENCE

IARC (1982) has classified 2,4,5-T and its esters in Group 3, chemicals that cannot be classified as to their carcinogenicity to humans, on the basis of inadequate evidence for carcinogenicity in humans and animals and inadequate evidence from short-term tests. It should be noted that IARC (1982) classified occupational exposure to phenoxy acid herbicides in Group 2B, probably carcinogenic to humans, on the basis of limited evidence for carcinogenicity in humans. Overall, the evidence for carcinogenicity of 2,4,5-T to animals may most appropriately be considered "inadequate." Using the U.S. EPA (1986b) guidelines, 2,4,5-T would be placed in Group D, meaning that current data are inadequate for the assessment of the potential carcinogenicity of 2,4,5-T.

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1988) recommended an RfD of 0.01 mg/kg/day for 2,4,5-T based on a NOEL of 3 mg/kg/day in a 2-year rat feeding study (Kociba et al., 1979) and a 3-generation rat feeding study (Smith et al., 1981). The LOAEL in both studies was 10 mg/kg/day, which caused increased urinary coproporphyrins and decreased neonatal survival, respectively.

NAS (1977) recommended an RfD of 0.1 mg/kg/day based on a NOAEL of 10 mg/kg/day in dogs. This NOAEL was based on the study by Drill and Hiratzka (1953) in which mongrel dogs were fed capsules containing 2, 5, 10 or 20 mg/kg/day 2,4,5-T 5 days/week for 13 weeks. Mortality occurred at 20 mg/kg/day.

Both ACGIH (1986) and OSHA (1983) have recommended a TLV-TWA of 10 mg/m³ for occupational atmospheric exposures to 2,4,5-T. This value is based on animal feeding studies and extensive use experience with the compound (ACGIH, 1986).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral. Data from several subchronic studies with 2,4,5-T suggest that 10 mg/kg/day is a NOEL and a suitable basis for deriving an oral RfD_{SO}. This dosage was a NOEL in the 13-week dog study by Drill and Hiratzka (1953) in which no adverse effects were observed in dogs receiving doses of 2.5 or 10 mg/kg/day, 5 days/week, while all dogs at 20 mg/kg/day died. NAS (1977) reported 90-day rat NOELs of 10, 18.6 and 30 mg/kg/day from various studies. Gehring and Betso (1978) described an unpublished 90-day study in which Sprague-Dawley rats receiving 30 mg/kg/day in the diet experienced increased liver and kidney weights and small but significant increases in SAP and SGPT levels, but no adverse effects occurred at 10 mg/kg/day. Although 10 mg/kg/day is not the highest NOEL below which no adverse effects have been reported, it appears to provide the best basis for RfD_{SO} derivation because the higher NOEL of 18.6 mg/kg/day for various esters of 2,4,5-T (Advisory Committee on 2,4,5-T, 1971; NAS, 1977) is very close to the 20 mg/kg/day level that was lethal to dogs (Drill and Hiratzka, 1953). The 10 mg/kg/day subchronic NOEL in rats (Gehring and Betso, 1978) is the best basis for deriving an RfD_{SO}. If this value is divided by an uncertainty factor of 100 to account for interspecies extrapolation and differences in individual sensitivity, the resulting RfD_{SO} is 0.1 mg/kg/day or 7 mg/day for a 70 kg human.

6.1.2. Inhalation. Subchronic inhalation data suitable for derivation of an RfD_{SI} could not be located in the available literature.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral. Several studies defined 3 mg/kg/day as a chronic oral NOEL. In the 2-year rat study by Kociba et al. (1979), mild kidney effects occurred at 10 mg/kg/day, but no adverse effects occurred at 3 mg/kg/day. In the 3-generation rat study by Smith et al. (1981), 3 mg/kg/day was a NOEL for reproductive and other toxic effects, while neonatal survival was reduced at 10 and 30 mg/kg/day. Several other reproduction/teratogenicity studies in rats, mice and other species support 3 mg/kg/day as a NOEL for these effects as well. Dividing the NOEL of 3 mg/kg/day from the Kociba et al. (1979) study by an uncertainty factor of 300 to account for interspecies extrapolation, deficiencies in the chronic toxicity data base and differences in individual human sensitivity results in an RfD_0 of 0.01 mg/kg/day or 0.7 mg/day for a 70 kg human.

CSs were calculated for several effects observed in the chronic toxicity and reproductive effects experiments with 2,4,5-T. Because of the rated severity of teratogenic and fetotoxic effects relative to chronic toxicity endpoints such as hyperplasia and increased organ weights, most of the highest CSs could be obtained using data from teratogenicity/reproductive effects studies. Because the contaminant TCDD is also known to cause these effects, however, only studies using 2,4,5-T samples of known low TCDD content were considered appropriate for CS calculations. These calculations are summarized in Table 6-1. The highest CS was obtained using data from the 2-year feeding study by Nuranyi-Kovacs et al. (1976) in which survival time was significantly reduced in male C3HF mice receiving 80 ppm in the diet, a level resulting in a dosage of ~12 mg/kg/day according to the authors. The calculated RV_d was 2.8, and the effect was assigned an RV_e of 10, resulting in a maximum CS of 28 (see Table 6-1).

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TABLE 6-1

Composite Scores for the Toxicity of 2,4,5-T by Oral Exposure

Species/Strain	Sex	Exposure Dosage	Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	Reference
SD rats	M,F	30 mg/kg/day in the diet for 2 years	359.1	1.67	Decreased body weight gain, increased relative kidney weight, liver hyperplasia and inflammation	4	6.8	Kociba et al., 1979
SD rats	M,F	10 mg/kg/day in the diet for 2 years	119.7	2.4	Increased urinary coproporphyrins, increased mineral deposits in renal pelvis	6	14.3	Kociba et al., 1979
SD rats	M,F	10 mg/kg/day in the diet for 3 generations	119.7	2.4	Reduced neonatal survival	10	23.8	Smith et al., 1981
CSWF mice	M	80 ppm diet for 2 years (12 mg/kg/day)	63.3	2.8	Decreased survival time	10	27.9	Nuranyi-Kovacs et al., 1976
NMRI mice	F	35 mg/kg/day on days 6-15 of gestation	18.5	3.6	Increased incidence of cleft palate in offspring	10	36.0	Roll, 1971
NMRI mice	F	8 mg/kg/day on days 6-15 of gestation	4.2	4.56	decreased fetal weight	8	36.5	Neubert and Dillmann, 1972

[a]Human MED calculated by multiplying the animal dose by an adjustment factor of the cube root of the ratio of animal to human body weight, assuming body weight of 0.35 kg for rats and 0.03 kg for mice, and expressing the result in mg/day for a 70 kg human.

07/14/89

6.2.2. Inhalation. The chronic inhalation toxicity data reviewed in Section 3.2.2. are not useful for quantitative risk assessment. In an epidemiology study, Suskind and Hertzberg (1984) observed decreased pulmonary functions, ulcers of the gastrointestinal tract and an increased incidence of chloracne in workers exposed to 2,4,5-T compared with controls, but exposure levels and duration of exposure were not quantified. Experiments with chronic exposure of laboratory animals could not be located in the available literature.

6.3. CARCINOGENIC POTENCY (q_1^*)

No quantitative estimates of carcinogenic potency have been made for 2,4,5-T because the issue of its carcinogenicity is still in doubt.

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APPENDIX

Summary Table for 2,4,5-T

	Species	Experimental Exposure/Dose	Effect	Reference Dose (RfD or RfD_S) (mg/day)	Reference
Inhalation					
RfD_{SI}		ID			
RfD_I		ID			
Oral					
RfD_{SO}	rat, dog	10 mg/kg/day for 90 days	higher doses caused mortality (dogs) or increased organ weights	7.0	Gehring and Betso, 1978
RfD_O	rat	3 mg/kg/day for 2 years	higher doses caused kidney histopathology	1E-2	Kociba etal., 1979; U.S. EPA, 1988
Maximum					
CS	mice	80 ppm diet for 2 years (12 mg/kg/day) (RV_d=2.8)	decreased survival time (RV_e=10)	RV_d=2.8 CS=28	Muranyi-Kovacs et al., 1976

ID = Inadequate data

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